JAMA | Review

Mpox Clinical Presentation, Diagnostic Approaches, and Treatment Strategies
A Review

Boghuma K. Titanji, MD; Aniruddha Hazra, MD; Jason Zucker, MD, MS

IMPORTANCE A global outbreak of clade IIb *Monkeypox virus* (MPXV) infections spread rapidly across at least 118 countries resulting in a Public Health Emergency of International Concern (PHEIC) from July 2022 to May 2023. This outbreak affected more than 99 000 persons worldwide and caused more than 33 000 infections and 60 deaths in the US. In 2024, there have been approximately 200 new infections per month in the US. On August 14, 2024, the World Health Organization declared mpox a PHEIC for a second time due to a rapid increase in infections with clade I MPXV in Central Africa.

OBSERVATIONS Mpox is primarily acquired through direct skin to skin contact with MPXV. With clade IIb MPXV, infections are most commonly associated with sexual activity among individuals who are gay, bisexual, and other men who have sex with men. After a median incubation period of 7 to 10 days, prodromal symptoms include fever (62%-72%), lymphadenopathy (56%-86%), myalgias (31%-55%), malaise (23%-57%), and headache (25%-55%). Skin lesions progress through 4 well-defined stages (macules, papules, vesicles, and pustules) over 2 to 4 weeks. Clade IIb MPXV is typically a self-limited illness with a low mortality rate (<0.2% in the US); however, severe illness and death may occur in immunocompromised individuals, especially those with advanced HIV (CD4 count <200 cells/μL). Mpox should be suspected in patients with potential exposure to MPXV who have skin lesions, and the diagnosis is confirmed with polymerase chain reaction testing of lesions. Management is supportive and focuses on skin care and symptom relief with analgesics. While no antiviral treatments are currently approved for mpox by the US Food and Drug Administration, several therapeutics, such as tecovirimat, brincidofovir, and vaccinia immune globulin intravenous, are available through expanded access programs or clinical trials. Vaccination with the 2-dose Modified Vaccinia Ankara-Bavarian Nordic vaccine is recommended for high-incidence populations and has an efficacy of 66% to 86%.

CONCLUSIONS AND RELEVANCE Mpox is a viral infection transmitted primarily through close skin to skin contact that typically causes a self-resolving illness but can result in severe illness and death in immunocompromised individuals. First-line therapy is supportive care, although patients with severe mpox infection may be treated with advanced therapeutics. Mpox vaccination is effective and, if available, should be offered to individuals at risk of exposure to mpox.

www.t.me/MemodiAppArticulos

Related article

CME at jamacmelookup.com

Author Affiliations: Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia (Titanji); Section of Infectious Diseases and Global Health, University of Chicago Medicine, Chicago, Illinois (Hazra); Howard Brown Health, Chicago, Illinois (Hazra); Division of Infectious Diseases, Columbia University Irving Medical Center, New York, New York (Zucker).

Corresponding Author: Jason Zucker, MD, MS, Division of Infectious Diseases, Columbia University Irving Medical Center, 622 W 168th St, 8th Floor, New York, NY 10032 (Jz2700@cumc.columbia.edu).

Section Editor: Kristin Walter, MD, Deputy Editor.

JAMA. doi:10.1001/jama.2024.21091
Published online October 14, 2024.

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024

SHOUT
SHARE
IT

Mpox (formerly known as monkeypox) is caused by *Monkeypox virus* (MPXV), a zoonotic orthopoxvirus closely related to variola and vaccinia viruses and first discovered in 1958 in a colony of research monkeys. The first human case was described in 1970 in the Democratic Republic of Congo. MPXV is a double-stranded DNA virus with a large genome (200 kilobase) encoding for 191 proteins. There are 2 main clades (distinct genetic lineages or subgroups) of the virus that have evolved from a common ancestral virus. Clade I is endemic to Central African countries and is historically associated with more severe disease; clade II is endemic to West African countries and historically associated with milder disease.[1]

In 2022, mpox caused by clade IIb MPXV spread worldwide, with the first confirmed case outside of endemic areas reported on May 6, 2022, and the first reported case in the US on May 17, 2022. Since then, more than 99 000 mpox clade IIb cases have been recorded across at least 118 countries, with more than 33 000 of these cases and 60 deaths in the US.[2] The clade II MPXV outbreak has predominantly occurred among individuals who are gay, bisexual, and other men who have sex with men, and 38% of cases have occurred in patients with HIV; however, infections in the US have been reported in individuals of all ages, sexes, genders, and sexual orientations.[3,4]

The clade II MPXV outbreak peaked outside of Africa in the summer of 2022, and the World Health Organization (WHO) declared its Public Health Emergency of International Concern (PHEIC) over on May 10, 2023.[5] By summer 2024, mpox in the US was limited to approximately 200 reported cases monthly. However, the WHO declared a second PHEIC for mpox on August 14, 2024, due to a rapid increase in infections with clade I MPXV in Central Africa.[5]

Prior to the 2022 mpox outbreak, research on mpox had been limited. The worldwide spread of clade IIb MPXV has provided increased information about this disease.[6] This review discusses the epidemiology, transmission, clinical presentation, assessment and diagnosis, prognosis, management and treatment, and prevention of mpox. Key questions and answers for clinicians are listed in **Box 1**.

Box 1. Commonly Asked Questions

1. Who Is at Risk for Mpox?

Anyone can acquire mpox. During the worldwide clade II outbreak, transmission most commonly occurred through sexual contact among individuals who are gay, bisexual, and other men who have sex with men. With clade Ia MPXV, transmission is thought to be driven by zoonotic exposure and subsequent household spread, with a substantial proportion of infections among children. With the emergence of the novel clade Ib MPXV, household spread and sexual transmission among people who are gay, bisexual, and other men who have sex with men as well as heterosexual networks are being described.

2. What Are Common Signs and Symptoms of Mpox?

Painful skin lesions that progress through 4 well-defined stages (macules, papules, vesicles, and pustules) over 2-4 weeks are a hallmark of mpox. Prodromal symptoms, including fever (62%-72%), lymphadenopathy (56%-86%), myalgias (31%-55%), malaise (23%-57%), and headache (25%-55%), can develop before or after the start of the rash. Symptoms such as proctitis (14%-36%) and pharyngitis (13%-36%) have commonly occurred during the clade IIb worldwide outbreak and may be the presenting symptom of mpox.

3. What Are Treatments Options for Patients Who Test Positive for Mpox?

First-line treatment for mpox is supportive care with pain control and wound care. Investigational agents may be used for individuals with severe mpox or for those at risk of severe disease. Patients should be counseled on transmission and instructed to isolate until the lesions have reepithelialized, which may take up to 21 days.

Methods

A PubMed search was performed for English-language publications of *mpox or monkeypox* published between January 1, 1975, and September 13, 2024. A total of 5168 abstracts were identified. We prioritized the inclusion of recent, high-quality evidence such as randomized clinical trials and observational longitudinal studies with larger sample sizes and longer follow-up periods. Governmental websites were searched to identify current mpox topic recommendations where published evidence was unavailable. A total of 111 citations were included, consisting of 1 randomized clinical trial, 59 observational studies, 9 basic science articles, 23 reviews, 13 government website pages, 4 case reports, 1 conference abstract, and 1 press release.

Discussion

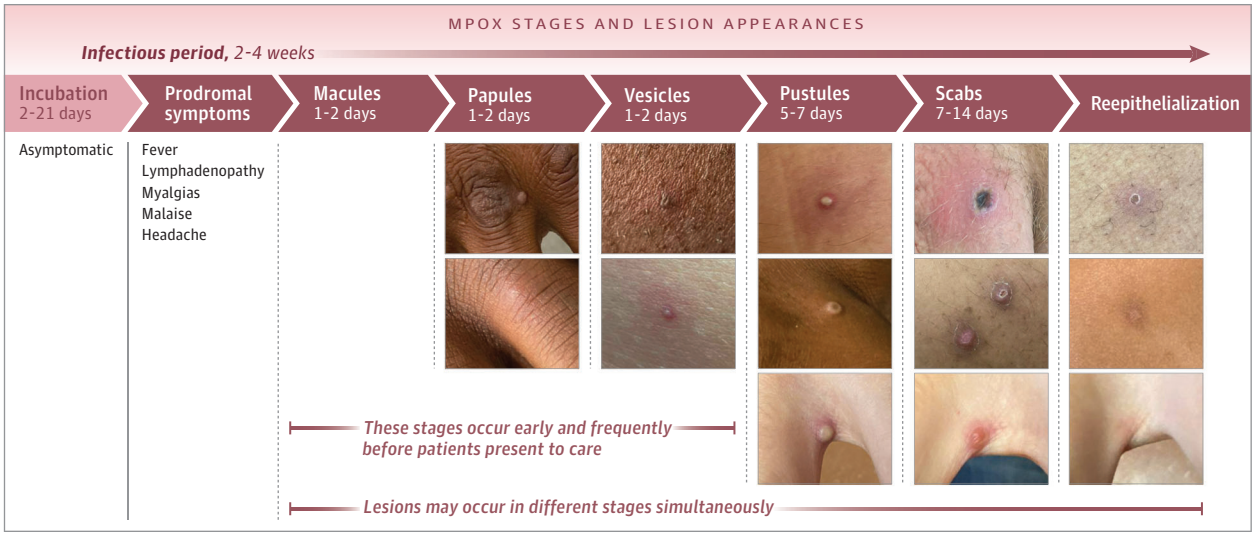
Transmission

The MPXV reservoir is thought to be arboreal rodents in African rainforests; most likely the squirrel *Funisciurus anerythrus*.[7] MPXV can be transmitted from animals to humans through direct contact with infected lesions, bodily fluids, bites, scratches, contaminated fomites such as linens and clothing, and respiratory droplets and aerosols. Close human to human contact has been the major driver of these outbreaks. Transmission via contaminated fomites and exposure to respiratory secretions are not major contributors.[8,9] While replication-competent MPXV has been found in the respiratory tract, there is no current evidence of human outbreaks in persons with shared airspace without direct contact with the virus.[9] Contact tracing of 113 cases associated with 221 commercial flights has resulted in no identified mpox infections.[10] In human to human transmission, the virus primarily spreads through direct prolonged contact with an infected person's lesions or bodily fluids.[9,11] There is also evidence that infected individuals can transmit the virus before exhibiting mpox symptoms and that asymptomatic transmission of MPXV may contribute to the spread of disease.[12-14] Acquisition of mpox through laboratory work is rare and has occurred primarily through needle-stick injuries, direct contact with an mpox specimen, or potentially through aerosols generated from laboratory procedures.

The transmission of MPXV primarily occurs when the virus enters the host through direct exposure to skin or mucosal surfaces, including oral, anogenital, or ocular tissues. The virus infects resident immune cells and local lymph nodes and rapidly replicates,[15] enabling the virus to spread through the lymphatic system and the bloodstream and disseminate to multiple organs.[15]

www.t.me/MemodiAppArticulos
© 2024 American Medical Association. All rights reserved.
Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024

Figure. Stages of Mpox and Lesion Examples



No nosocomial infections of hospitalized patients have been reported in the US, but nosocomial transmission has occurred in Africa.[16] A systematic review reported only 10 cases of nosocomial transmission to clinicians worldwide during the 2022 global outbreak, occurring primarily through injuries with sharp objects such as scalpels or needles.[17] Transmission to health care workers during the clade IIb outbreak has rarely occurred even when proper personal protective equipment (gown, gloves, eye protection, N95 respirator) was not used. Data from a facility in Colorado showed that despite low personal protective equipment usage and limited use of postexposure prophylaxis vaccination, none of 313 clinicians exposed in the course of routine patient care acquired mpox.[18]

Patients presenting for medical care who are suspected of having mpox should be placed in a single room and standard cleaning and disinfection procedures should be performed after the visit using an Environmental Protection Agency–registered hospital-grade disinfectant with an emerging viral pathogen claim.[19] Patients with mpox do not require airborne isolation. Nonhospitalized patients with mpox or suspected mpox should isolate at home. If mpox infection is confirmed, individuals should remain in isolation until all lesions have healed and reepithelialized.

Epidemiology

Prior to 2022, cases outside of Africa were rare and typically linked to international travel or the importation of infected animals. However, the 2022 global outbreak of clade IIb was largely spread through sexual transmission and contained in the sexual networks of individuals who are gay, bisexual, and other men who have sex with men. Over the past several months, subclade Ib has emerged in the South Kivu province of the Democratic Republic of the Congo (DRC); its rapid human to human transmission has occurred through close contact within households as well as sexual contact among both heterosexual people in addition to individuals who are gay, bisexual, and other men who have sex with men.[20]

Clinical Presentation

Mpox can vary widely from a mild, self-limiting illness to a severe disease with life-threatening complications in immunocompromised individuals.[21-23] While the mean incubation period of mpox ranges from 2 to 21 days, the mean incubation period during the clade IIb outbreak, characterized largely by sexual transmission, typically ranged from 7 to 10 days.[24-28]

Following an asymptomatic incubation period, patients with mpox typically have a prodrome of symptoms for 1 to 5 days including fever (62%-72%), lymphadenopathy (56%-86%), myalgias (31%-55%), malaise (23%-57%), and headache (25%-55%)[24,27-33] before the appearance of a rash.[23] However, during the 2022 clade IIb outbreak, the timing of prodromal symptoms was variable, occurring before, during, or after the appearance of the rash or other presenting symptoms (eg, proctitis).[28,30]

The characteristic clinical feature of mpox is painful skin lesions that uniformly progress through 4 well-defined stages over 2 to 4 weeks, as shown in the **Figure**. Lesions typically begin as macules and evolve into papules, vesicles, and pustules, which crust and desquamate in the final stage. People with mpox are infectious from the onset of clinical symptoms until all skin lesions have reepithelialized, typically taking up to 4 weeks.

The mpox rash classically occurs in a centrifugal distribution, with lesions involving the face, trunk, and limbs. However, transmission through sexual contact, as observed in the recent global outbreak, has frequently caused genital and anogenital (36%-73%) and perioral and oral skin lesions (14%-25%), associated painful lesions at any mucosal site, nonuniform progression of lesions (eg, different stages of lesions side by side), and limited (median number of 10) lesions.[27,28,30,34] Mpox has also presented with other complications, including proctitis (14%-36%), pharyngitis (13%-36%), urethritis, and ocular disease.[27,28,30,34] Less than 5% of patients with mpox present with a single skin lesion without other symptoms or with mucosal symptoms (proctitis/pharyngitis) without skin lesions.[23,24,26] Localized single lesions at the point of a needlestick injury have also been described in health care workers.[35]

Severe Disease and Complications

Mpox can cause complications, such as necrotizing skin lesions with bacterial superinfection, pneumonia, and encephalitis, particularly in immunocompromised individuals such as those with advanced

www.t.me/MemodiAppArticulos
© 2024 American Medical Association. All rights reserved.
Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024

Table 1. Major Epidemiologic and Burden of Disease Facts

Mpox features	Clade I	Emerging clade Ib	Clade IIa	Clade IIb
Primary geographical distribution	Central Africa	Democratic Republic of Congo	West Africa	Global outbreak involving at least 118 countries
Spread	Introduction into the human population typically through zoonotic transmission event. Mainly children and close household contacts of infected persons	The spread was described in heterosexual networks and case clusters in the Democratic Republic of Congo, with 30% of the population being adult females Accumulation of APOBEC3 variations, which signify recent sustained human to human transmission	Households with families and children are frequently affected	Primarily close physical contact between gay, bisexual, and other men who have sex with men
Severity of disease	Mortality, 5%-10% (outbreaks prior to 2022)	Mortality, 1.7%-3.6%	Mortality, 1%	Mortality <0.1%, primarily immunocompromised persons

Abbreviation: APOBEC3, apolipoprotein B editing complex.

HIV (CD4 count <200 cells/μL). Abnormal liver function test results are common, seen in more than one-third of hospitalized patients with mpox.[36] Compared with immunocompetent individuals, people with advanced HIV or solid organ transplants have a higher likelihood of developing multiorgan involvement with mpox infection, resulting in a substantially higher need for hospitalization and increased risk of death.[37-40] This increased susceptibility to severe disease is due in part to an inadequate innate immune response characterized by impaired natural killer cell and T-lymphocyte function and inadequate B-cell responses, which are important to clear the virus.[40]

More severe mpox infections have been described in young children and pregnant individuals in clade I outbreaks; however, fewer cases from these groups have been described in the clade IIb outbreak.[23,24,31,41-43]

Diagnosis

The diagnosis of mpox should be suspected in patients with skin lesions and known or possible exposure to MPXV. The typical appearance includes painful skin lesions covering multiple regions in any of the 4 stages previously described, while an atypical presentation includes exanthem and/or a single, painless, or ulcerated lesion. Diagnostic confirmation is achieved through molecular DNA amplification techniques of samples collected from lesions to detect MPXV. For initial testing of suspected mpox, a nonvariola orthopoxvirus polymerase chain reaction (PCR) test of skin lesions is frequently used. Confirmatory, clade-specific testing, which can be performed by the US Centers for Disease Control and Prevention (CDC), should be considered if the initial test result is positive or inconclusive. In the US, mpox is a reportable disease to local health departments.

The CDC recommends that clinicians wear a gown, gloves, eye protection, and an N95 respirator while testing for mpox to protect against viral transmission.[19] At least 2 skin lesions should be sampled from separate sites, if possible, using a sterile synthetic swab. The lesion must be vigorously swabbed to ensure an adequate collection of viral DNA; unroofing or aspiration of lesions with a scalpel or needle tip is not advised due to the risk of self-injury. Swabs may be stored dry or in virus transport media, as specified by the diagnostic laboratory.[44]

Several reverse transcriptase PCR testing options are available in the US for detecting the clade II virus. These tests use primers and probes that target highly conserved regions of the viral genome.[45] Patients who test positive on a screening orthopoxvirus PCR test and negative on a clade II–specific PCR test may have a clade I MPXV infection or infection with another less common pathogenic orthopoxvirus infection such as cowpox or Borealpox (formerly Alaskapox). In such cases, samples should be forwarded to a reference laboratory, such as the CDC, for further testing. Viral culture and phenotyping assays to determine antiviral susceptibility are not routinely performed for clinical care but may be performed for epidemiological and research purposes.

In 2023, the US Food and Drug Administration (FDA) authorized point-of-care testing modalities, including real-time PCR tests for clade IIb and nonvariola orthopoxvirus, on a commercial platform that performs as well as laboratory-based assays.[46,47] These point-of-care tests provide rapid results (typically within 36 minutes) and are especially useful during outbreaks because they require minimal training. Furthermore, on April 10, 2024, the FDA granted Emergency Use Authorization for a home self-collection sampling kit, which may help overcome barriers to testing and the stigma associated with mpox testing.[48]

Orthopoxvirus serology testing is rarely performed because of the increased likelihood for false-positive results due to cross-reactivity with other orthopoxviruses. Positive serology could represent prior exposure to the vaccinia virus either through vaccination with available smallpox or mpox vaccines, many of which were administered during the 2022 mpox outbreak, or from a previous infection or active infection with another orthopox virus.[49]

Differential Diagnosis

The differential for mpox includes several other infections that involve skin and mucosal lesions. Secondary syphilis may present with a generalized rash and mucocutaneous lesions, but unlike mpox, these lesions are generally painless. Herpes simplex virus can present with painful vesicular lesions, particularly in the anogenital area, which may resemble mpox. Other skin and soft tissue infections, such as impetigo or cellulitis, can present with pustular or vesicular lesions that may appear similar to mpox.[50] In children and occasionally adults, enteroviral infection, molluscum contagiosum, varicella-zoster virus, and other orthopoxviruses should be considered in the differential diagnosis of mpox.

Prognosis

Most individuals with mpox experience a self-limiting illness and typically recover fully within 2 to 4 weeks after onset of symptoms.

www.t.me/MemodiAppArticulos
© 2024 American Medical Association. All rights reserved.
Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024

Table 2. Supportive Care Recommendations for Mpox

	Skin (including genital) lesions	Proctitis	Pharyngitis
Supportive care recommendations	Lidocaine gel Nonsteroidal anti-inflammatory medications Opioids (if indicated) Keep lesions clean and dry If infected: Debridement with wet-to-dry dressings Antibiotics	Lidocaine gel Nonsteroidal anti-inflammatory medications Opioids (if indicated) Stool softeners Sitz baths Gabapentin	Viscous lidocaine Nonsteroidal anti-inflammatory medications Opioids (if indicated) Saltwater gargles Oral antiseptics

Table 3. Potential Medical Treatments for Mpox

	Trifluridine	VIGIV	Cidofovir	Brincidofovir	Tecovirimat
Route	Eye drops	IV	IV	Oral	Oral/IV
Adult dosing	One drop per eye	6000-9000 units/kg	5 mg/kg	200 mg	600 mg/200 mg
Frequency	Every 2 h for 2 wk	Single dose but may be repeated in prolonged illness	Weekly	Weekly	Twice daily/ 3 times daily
Duration[a]	Up to 4 wk		2 wk	2 wk	2 wk
Serious adverse effects reported	Topical effects on the eye have been reported	Anaphylaxis, volume overload	Nephrotoxicity	Elevated liver enzymes, diarrhea inhibiting absorption of other medications	Contraindicated when CrCl <30 mL/min
Availability	Commercially available	CDC EA-IND	Commercially available	FDA EA-IND	STOMP trial/ CDC EA-IND

Abbreviations: CDC, Centers for Disease Control and Prevention; CrCl, creatine clearance; EA-IND, Expanded Access for an Investigational New Drug; FDA, Food and Drug Administration; IV, intravenous; STOMP, Study of Tecovirimat for Human Mpox Virus; VIGIV, vaccinia immune globulin intravenous.

[a] Duration may be extended in severe infection and immunocompromised individuals with ongoing disease.

After healing, mpox skin lesions can leave scars (5%-40% of people infected with mpox), potentially causing stigmatizing cosmetic effects and more commonly affecting those with advanced HIV.[51-53] Genital lesions due to mpox may result in long-term complications such as scarring and strictures in anogenital areas, which can significantly affect quality of life and sexual function.[51] Ocular involvement is a serious complication of mpox and can sometimes result in partial vision loss or even blindness, therefore, early ophthalmology evaluation is encouraged.[54] Less common complications may include urethral strictures and paraphimosis, as well as rectal perforations, fistulas, and strictures.[27,30,55-57] In these cases, involvement of urology and colorectal surgery specialists may be beneficial.

The mortality rate during the clade IIb global outbreak from 2022 to the present has been low in high-income countries (<0.2% in the US).[2] However, the overall mortality rate in prior mpox outbreaks in Africa was 4.6% and data from the DRC showed a mortality rate of 1.67% in the context of optimal supportive medical care, including nutrition, hydration, and treatment for secondary infections.[58,59] This disparity in outcomes between the US and countries in Africa may be due to better access to supportive care and nutrition in high-income countries. Additionally, prior outbreaks in Africa have disproportionately affected children, who may be more vulnerable to severe disease outcomes.[31]

The severity of mpox and its clinical outcomes are influenced by virus-specific virulence factors and immune escape properties, as well as by host immune status and response to infection. Severity can be challenging to compare across clades and between outbreaks occurring in different locations due to differences in baseline health and access to health care services among affected populations. However, compared with clade IIb, infections with the clade I virus are associated with a more severe disease course, and higher mortality rates (up to 10%) have been reported during outbreaks in the DRC.[8,23,47-49] Experimental studies in small animal models using different viral subclades (clade I, clade IIa, and clade IIb) have demonstrated these differences in virulence across clades (**Table 1**).[60,61]

Management and Treatment

While no treatments are specifically approved by the FDA for mpox, several antiviral medications used for other orthopoxviruses have been used for patients with severe mpox infections.

Supportive Care

Most patients with mpox experience pain due to skin and mucosal lesions. The CDC offers guidance for supportive care and pain management.[62] Oral medications, such as acetaminophen or nonsteroidal anti-inflammatory drugs, are recommended for pain control. Patients with mpox who have more severe pain may be treated with gabapentinoids or short courses of opioids.[63,64] Stool softeners help decrease painful bowel movements associated with proctitis. Topical treatments, such as sitz baths or lidocaine gels for proctitis and saltwater or viscous lidocaine gargles for pharyngitis, may decrease pain. For suspected bacterial superinfection of mpox lesions, topical or systemic antibiotics indicated for skin and soft tissue infections are advised (**Table 2**).

All individuals assessed for mpox should also be screened for sexually transmitted infections (gonorrhea, chlamydia, syphilis,

www.t.me/MemodiAppArticulos
© 2024 American Medical Association. All rights reserved.
Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024

Box 2. ACIP Recommendation for Mpox Vaccination

Recommendation

ACIP recommends vaccination with the 2-dose MVA-BN vaccine series for persons aged 18 years and older at risk for mpox[a]

Definition of Persons at Risk per the CDC

People who are gay, bisexual, and other men who have sex with men, as well as transgender or nonbinary people who in the past 6 months have had 1 of the following:

- A new diagnosis of ≥1 sexually transmitted disease
- More than 1 sex partner
- Sex at a commercial sex venue
- Sex in association with a large public event in a geographic area where mpox transmission is occurring

Sexual partners of persons with the risks described above

Persons who anticipate experiencing any of the above

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; MVA-BN, Modified Vaccinia Ankara Vaccine-Bavarian Nordic.

[a] MVA-BN vaccination is available for children and adolescents younger than 18 years determined to be at high risk for MPVX infection under an Emergency Use Authorization.

and HIV) because of the high incidence of coinfection reported in multiple cohorts during the 2022 mpox outbreak.[3,4,28-30,34,38]

Medical Treatment

Currently, there are no FDA-approved treatments for mpox. Several agents have been used for mpox that were approved for smallpox through the FDA Animal Rule, which allows efficacy findings from animal studies when human trials are not ethical or feasible (**Table 3**).

Tecovirimat

Tecovirimat, which is FDA approved for smallpox through the Animal Rule, targets the p37 protein, which is involved in development of the viral envelope required for replication in orthopoxviruses. In the US, more than 7000 individuals with mpox have received tecovirimat under an Expanded Access for an Investigational New Drug (EA-IND) protocol, with limited available safety data indicating only mild adverse effects.[65] Observational data on the effectiveness of tecovirimat has shown mixed results.[66-69] In 2024, a randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of oral tecovirimat for the treatment of mpox was completed; preliminary results indicated that tecovirimat did not reduce the duration of mpox lesions among 597 children and adults with clade I MPXV in the DRC.[58] Tecovirimat is available for treatment of mpox for all patients in the US through the Study of Tecovirimat for Human Mpox Virus (STOMP) clinical trial, and through a CDC EA-IND for those with severe disease or at risk of severe disease.[62] Phenotypic resistance (reduced activity) to tecovirimat has been described most commonly among immunocompromised patients receiving prolonged courses of treatment, likely due to tecovirimat resistance mutations in the *F13L* gene of the mpox virus, which is crucial for viral maturation and dissemination.[70] Transmitted drug resistance has also been observed.[70-72]

Cidofovir and Brincidofovir

Cidofovir and its prodrug brincidofovir are antiviral medications that inhibit DNA polymerase activity and, thus, DNA replication. Although no randomized efficacy data exist in humans, animal models suggest that brincidofovir may be effective against orthopoxviruses, including mpox. Data for cidofovir use are extrapolated from the data for brincidofovir.[73]

Intravenous cidofovir has been used to treat highly immunosuppressed patients with severe mpox disease.[73] Cidofovir has also been used topically as a cream for skin lesions or directly injected into skin lesions, with some case studies reporting clinical improvement.[74] Cidofovir is FDA approved for cytomegalovirus retinitis and therefore is widely available in the US and several other high-income countries for off-label use.

Brincidofovir, a prodrug of cidofovir, is less nephrotoxic. Its adverse effects are primarily transaminitis and diarrhea, which can interfere with the absorption of oral medications.[75] Animal studies have suggested that brincidofovir alone may be effective, and in vitro there may also be a synergistic effect when combined with tecovirimat.[76] Brincidofovir is FDA approved for smallpox, but is available for treatment of mpox through an FDA EA-IND.[62] The CDC recommends consideration of combination therapy with tecovirimat and brincidofovir for severely immunocompromised individuals with severe mpox infection.[73]

Vaccinia Immune Globulin Intravenous

Vaccinia immune globulin intravenous (VIGIV) treatment is the administration of antibodies targeting vaccinia virus, which may provide activity against the MPXV virus. There are no published data currently available on the effectiveness of VIGIV for the treatment of mpox virus in humans. VIGIV may be considered for patients with severe mpox and advanced HIV, who may be unable to produce an adequate antibody response to infection.[73,77] VIGIV is available for the treatment of mpox through a CDC EA-IND.[62]

Trifluridine

The topical antiviral agent trifluridine has in vitro activity against orthopoxviruses and has been provided to patients with mpox ocular disease, although there are limited observational data on its efficacy.[78]

Combinations of these treatments have been used in severely ill patients with mpox; however, no clinical trial data have demonstrated the effectiveness of combination therapies for mpox.

Prevention

Behavioral Changes

After the start of the 2022 mpox outbreak, people vulnerable to mpox infection, particularly individuals who are gay, bisexual, and other men who have sex with men, adjusted their behaviors to reduce mpox transmission, including reducing the number of sexual partners and frequency of sexual encounters.[78] Modeling data suggest that the 2022 outbreak was slowed first through self-protective behavioral changes among populations with increased exposure risk, followed by vaccination.[78]

Vaccination

Two vaccines have been approved by the FDA and are available for the prevention of mpox in adults: ACAM2000, a second-generation,

www.t.me/MemodiAppArticulos
© 2024 American Medical Association. All rights reserved.
Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024

Table 4. Observational Vaccine Efficacy Studies

Source	Vaccine	% (95% CI)[a] 1-Dose efficacy	2-Dose efficacy	Evaluation period
Fine et al,[86] 1988	Dryvax	85		1980 to 1984
Rimoin et al,[87] 2010	Dryvax	80.7 (68.2 to 88.4)		Nov 2005 to Nov 2007
Titanji et al,[88] 2023	Dryvax	72 (32 to 87)		Jul 1, 2022, to Oct 31, 2022
	ACAM2000	75 (68 to 85)		
Back et al,[89] 2024	MVA-BN	70 (44 to 84)	89 (12 to 99)	Aug 1, 2022, to Sep 30, 2022
Bertran et al,[90] 2023	MVA-BN	78 (54 to 89)		Jul 4, 2022, to Oct 9, 2022
Brousseau et al,[91] 2024	MVA-BN	35 (−2 to 59) 65 (1 to 87)[b]		Jun 19, 2022, to Jun 2, 2022
Charles et al,[92] 2024	MVA-BN		80	Jan 1, 2023, to Dec 31, 2023
Dalton et al,[93] 2023	MVA-BN	75 (61.2 to 84.2)	86 (73.8 to 92.4)	Aug 19, 2022, to Mar 31, 2023
Deputy et al,[94] 2023	MVA-BN	35.8 (22.1 to 47.1)	66 (47.4 to 78.1)	Aug 15, 2022, to Nov 19, 2022
Fontán-Vela et al[95] 2024	MVA-BN	79 (33.3 to 100)		Jul 12, 2022, to Dec 12, 2022
Navarro et al,[96] 2024	MVA-BN	58 (31 to 75)		Jun 2022 to Nov 2022
Ramchandani et al,[97] 2023	MVA-BN	81 (64 to 90)	83 (28 to 96)	Jan 1, 2020, to Dec 31, 2022
Rosenberg et al,[98] 2023	MVA-BN	68.1 (24.9 to 86.5)	75.7 (48.5 to 88.5)	Jul 24, 2022, to Oct 31, 2022
Wolff Sagy et al,[99] 2023	MVA-BN	86 (59 to 95)		Jul 31, 2022, to Dec 25, 2022
Yeganeh et al,[100] 2024	MVA-BN	69 (59 to 77)	85 (80 to 87)	May 19, 2022, to Jan 1, 2023

Abbreviation: MVA-BN, Modified Vaccinia Ankara Vaccine-Bavarian Nordic.

[a] All results are adjusted results for disease acquisition at ≥14 days after vaccination unless otherwise specified.

[b] Includes adjustment for self-reported risk.

replication-competent, single-dose smallpox vaccine and Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN; also known as IMVANEX, IMVAMUNE, and JYNNEOS), a third-generation, replication-limited smallpox and mpox vaccine.[79] The MVA-BN vaccine (JYNNEOS), which became commercially available in the US in April 2024, is administered subcutaneously or intradermally in 2 doses given 4 weeks apart. Due to its high cost, MVA-BN access has been limited for individuals who do not have insurance or are underinsured in the US, and access to mpox vaccine has also been very limited in low- and middle-income countries, including those with large and emerging mpox outbreaks. In September 2024, the WHO announced MVA-BN as the first vaccine against mpox to be included in its prequalification list, which will accelerate procurement of mpox vaccines by governments and international agencies and is expected to increase access to mpox vaccinations in low- and middle-income countries.[80]

Preexposure Prophylaxis

The Advisory Committee on Immunization Practices recommends vaccination with the 2-dose series of MVA-BN as preexposure prophylaxis for people aged 18 years and older at nonoccupational risk for mpox,[81] including people who are gay, bisexual, and other men who have sex with men, as well as transgender or nonbinary people, who in the past 6 months have been newly diagnosed with 1 or more sexually transmitted diseases, had multiple sex partners, engaged in sex at a commercial venue or during a large public event in an area where mpox transmission is occurring, or are sexual partners of those who meet these criteria. This also applies to individuals who anticipate engaging in any of these activities. There are no recommendations from the Advisory Committee on Immunization Practices regarding mpox vaccination booster doses for those with nonoccupational risk of exposure (Box 2).

MVA-BN and ACAM2000 can be used for preexposure prophylaxis vaccination for people at occupational risk for exposure to mpox, such as laboratory workers. Individuals at risk of occupational exposure (laboratory setting) are advised to receive an MVA-BN booster every 2 years or an ACAM2000 booster every 3 years.[79] Vaccination is not routinely recommended for clinicians providing care for patients with mpox who have access to appropriate personal protective equipment.[79]

A growing body of evidence indicates that while vaccination is not fully protective against mpox, breakthrough infections tend to be milder and are less likely to lead to hospitalization or death (Table 4).[82-85] Vaccination with the 2-dose MVA-BN vaccine is recommended for specific populations and has an efficacy rate of 66% to 86% (Box 2).[86-100] Long-term vaccine effectiveness and duration of immunity provided by MVA-BN against mpox remain uncertain.[101]

Postexposure Prophylaxis

The CDC recommends MVA-BN vaccination as postexposure prophylaxis for people with known or presumed exposure to mpox, ideally administered within 4 days of exposure but can be given up to 14 days after exposure. There are limited observational data on the effectiveness of postexposure prophylaxis vaccination for mpox.[102,103]

Clade I MPXV and Its Global Implications

While mpox clade IIb MPXV infections in Europe and North America have decreased from the peak in the summer of 2022, several African countries continue to have frequent and large outbreaks of mpox and the emergence of new viral clades. In 2024, the DRC experienced the largest recorded outbreak of clade I MPXV, with more than 21 000 suspected cases and more than 700 deaths.[104] This outbreak includes a cluster of cases involving sexual transmission of the clade I virus, creating concern for widespread transmission through

www.t.me/MemodiAppArticulos
© 2024 American Medical Association. All rights reserved.
Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024

social and sexual contact similar to the clade IIb outbreak in 2022 but mostly involving heterosexual networks, although spread among people who are gay, bisexual, and other men who have sex with men has also been reported.[51]

A recent investigation into a cluster of mpox cases in eastern DRC from September 2023 to January 2024 identified a novel emerging strain named clade Ib.[105,106] This strain shows significant genetic divergence from clade Ia viral sequences isolated from previous outbreaks with accumulation of apolipoprotein B editing complex (APOBEC3)–mediated mutations, suggesting that direct transmission between humans, rather than animal to human transmission, is becoming the predominant mode of spread for mpox in large outbreaks.[106-108] The emergence of clade Ib MPXV and its rapid spread in the DRC and neighboring countries (Burundi, Kenya, Rwanda, and Uganda) underscores the need for heightened surveillance and global vaccine equity to mitigate an ongoing public health crisis.[109] In response to this global health concern, in August 2024, the WHO declared mpox a PHEIC. As of August 25, 2024, clade Ib cases were reported in Sweden (n = 1) and Thailand (n = 1) after travel to Africa.[110]

Limitations

This review has several limitations. First, the quality of the included literature was not formally evaluated. Second, some relevant studies may have been missed. Third, it does not cover all aspects of mpox transmission, clinical presentation, assessment and diagnosis, prognosis, management and treatment, and prevention. Fourth, mpox is rapidly evolving.

Conclusions

Mpox is a viral infection transmitted primarily through close skin contact that typically causes a self-resolving illness but can result in severe illness and death in immunocompromised individuals. First-line therapy is supportive care, although patients with severe mpox infection may be treated with advanced therapeutics. Mpox vaccination is effective and, if available, should be offered to individuals at risk of exposure to mpox. Mpox is an evolving global health threat, and clinicians must be aware of characteristic signs and symptoms of mpox to ensure timely diagnosis and appropriate management.

ARTICLE INFORMATION

Accepted for Publication: September 19, 2024.

Published Online: October 14, 2024. doi:10.1001/jama.2024.21091

Conflict of Interest Disclosures: Dr Titanji reported receiving grants from the National Institutes of Health's Building Interdisciplinary Research Careers in Women's Health and Emory Center for AIDS Research. Dr Zucker reported receiving grants from the Centers for Disease Control and Prevention and serving as vice chair of the STOMP trial. No other disclosures were reported.

Additional Contributions: We thank Stephanie Galitano, MD, Columbia University Vagelos College of Physicians and Surgeons, for her gracious effort in reviewing images for the figure.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

REFERENCES

1. Lansiaux E, Jain N, Laivacuma S, Reinis A. The virology of human monkeypox virus (hMPXV): a brief overview. *Virus Res*. 2022;322:198932. doi:10.1016/j.virusres.2022.198932

2. Centers for Disease Control and Prevention. Mpox: ongoing 2022 global outbreak cases and data. Accessed May 1, 2024. https://archive.cdc.gov/#/details?q=https://www.cdc.gov/poxvirus/mpox/response/2022/index.html

3. Kava CM, Rohraff DM, Wallace B, et al. Epidemiologic features of the monkeypox outbreak and the public health response—United States, May 17-October 6, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(45):1449-1456. doi:10.15585/mmwr.mm7145a4

4. Curran KG, Eberly K, Russell OO, et al; Monkeypox, HIV, and STI Team. HIV and sexually transmitted infections among persons with monkeypox—eight US jurisdictions, May 17-July 22, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(36):1141-1147. doi:10.15585/mmwr.mm7136a1

5. Centers for Disease Control and Prevention. National notifiable infectious diseases and conditions, United States: weekly tables. Accessed September 14, 2024. https://wonder.cdc.gov/nndss/nndss_weekly_tables_menu.asp

6. McQuiston JH, Braden CR, Bowen MD, et al. The CDC domestic mpox response—United States, 2022-2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(20):547-552. doi:10.15585/mmwr.mm7220a2

7. Curaudeau M, Besombes C, Nakouné E, Fontanet A, Gessain A, Hassanin A. Identifying the most probable mammal reservoir hosts for monkeypox virus based on ecological niche comparisons. *Viruses*. 2023;15(3):727. doi:10.3390/v15030727

8. Pan D, Nazareth J, Sze S, et al. Transmission of monkeypox/mpox virus: a narrative review of environmental, viral, host, and population factors in relation to the 2022 international outbreak. *J Med Virol*. 2023;95(2):e28534. doi:10.1002/jmv.28534

9. Beeson A, Styczynski A, Hutson CL, et al. Mpox respiratory transmission: the state of the evidence. *Lancet Microbe*. 2023;4(4):e277-e283. doi:10.1016/S2666-5247(23)00034-4

10. Delea KC, Chen TH, Lavilla K, et al. Contact tracing for mpox clade II cases associated with air travel—United States, July 2021-August 2022. *MMWR Morb Mortal Wkly Rep*. 2024;73(35):758-762. doi:10.15585/mmwr.mm7335a1

11. Lee BU. Airborne transmission of MPXV and its aerosol dynamics under different viral load conditions. *Lancet Microbe*. 2023;4(5):e288-e289. doi:10.1016/S2666-5247(23)00059-9

12. De Baetselier I, Van Dijck C, Kenyon C, et al; ITM Monkeypox study group. Retrospective detection of asymptomatic monkeypox virus infections among male sexual health clinic attendees in Belgium. *Nat Med*. 2022;28(11):2288-2292. doi:10.1038/s41591-022-02004-w

13. Miura F, Backer JA, van Rijckevorsel G, et al; Dutch Mpox Response Team. Time scales of human mpox transmission in the Netherlands. *J Infect Dis*. 2024;229(3):800-804. doi:10.1093/infdis/jiad091

14. Brosius I, Van Dijck C, Coppens J, et al; ITM MPOX Study Group. Presymptomatic viral shedding in high-risk mpox contacts: a prospective cohort study. *J Med Virol*. 2023;95(5):e28769. doi:10.1002/jmv.28769

15. Lum FM, Torres-Ruesta A, Tay MZ, et al. Monkeypox: disease epidemiology, host immunity and clinical interventions. *Nat Rev Immunol*. 2022;22(10):597-613. doi:10.1038/s41577-022-00775-4

16. Petersen BW, Kabamba J, McCollum AM, et al. Vaccinating against monkeypox in the Democratic Republic of the Congo. *Antiviral Res*. 2019;162:171-177. doi:10.1016/j.antiviral.2018.11.004

17. Zachary KC, Philpotts LL, Shenoy ES. Mpox exposure and transmission in healthcare settings during the 2022 global outbreak. *Curr Opin Infect Dis*. 2023;36(4):257-262. doi:10.1097/QCO.0000000000000933

18. Marshall KE, Barton M, Nichols J, et al; Colorado Healthcare Personnel Monitoring Team. Health care personnel exposures to subsequently laboratory-confirmed monkeypox patients—Colorado, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(38):1216-1219. doi:10.15585/mmwr.mm7138e2

19. Centers for Disease Control and Prevention. Mpox infection prevention and control in healthcare settings. Accessed September 21, 2024. https://www.cdc.gov/mpox/hcp/infection-control/healthcare-settings.html

20. World Health Organization. Disease outbreak news: mpox—African region. Accessed August 29, 2024. https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON528

21. Gessain A, Nakoune E, Yazdanpanah Y. Monkeypox. *N Engl J Med*. 2022;387(19):1783-1793. doi:10.1056/NEJMra2208860

22. Titanji BK, Tegomoh B, Nematollahi S, Konomos M, Kulkarni PA. Monkeypox: a contemporary review for healthcare

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024

professionals. *Open Forum Infect Dis*. 2022;9(7):ofac310. doi:10.1093/ofid/ofac310

23. Mitjà O, Ogoina D, Titanji BK, et al. Monkeypox. *Lancet*. 2023;401(10370):60-74. doi:10.1016/S0140-6736(22)02075-X

24. Huhn GD, Bauer AM, Yorita K, et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. *Clin Infect Dis*. 2005;41(12):1742-1751. doi:10.1086/498115

25. Minhaj FS, Ogale YP, Whitehill F, et al; Monkeypox Response Team 2022. Monkeypox outbreak—nine states, May 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(23):764-769. doi:10.15585/mmwr.mm7123e1

26. Miura F, van Ewijk CE, Backer JA, et al. Estimated incubation period for monkeypox cases confirmed in the Netherlands, May 2022. *Euro Surveill*. 2022;27(24):2200448. doi:10.2807/1560-7917.ES.2022.27.24.2200448

27. Tarín-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. *Lancet*. 2022;400(10353):661-669. doi:10.1016/S0140-6736(22)01436-2

28. Thornhill JP, Barkati S, Walmsley S, et al; SHARE-net Clinical Group. Monkeypox virus infection in humans across 16 countries—April-June 2022. *N Engl J Med*. 2022;387(8):679-691. doi:10.1056/NEJMoa2207323

29. Philpott D, Hughes CM, Alroy KA, et al; CDC Multinational Monkeypox Response Team. Epidemiologic and clinical characteristics of monkeypox cases—United States, May 17-July 22, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(32):1018-1022. doi:10.15585/mmwr.mm7132e3

30. Patel A, Bilinska J, Tam JCH, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. *BMJ*. 2022;378:e072410. doi:10.1136/bmj-2022-072410

31. Ježek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. *J Infect Dis*. 1987;156(2):293-298. doi:10.1093/infdis/156.2.293

32. McCollum AM, Damon IK. Human monkeypox. *Clin Infect Dis*. 2014;58(2):260-267. doi:10.1093/cid/cit703

33. Petersen E, Kantele A, Koopmans M, et al. Human monkeypox: epidemiologic and clinical characteristics, diagnosis, and prevention. *Infect Dis Clin North Am*. 2019;33(4):1027-1043. doi:10.1016/j.idc.2019.03.001

34. Thornhill JP, Palich R, Ghosn J, et al; Share-Net writing Group. Human monkeypox virus infection in women and non-binary individuals during the 2022 outbreaks: a global case series. *Lancet*. 2022;400(10367):1953-1965. doi:10.1016/S0140-6736(22)02187-0

35. Choi Y, Jeon EB, Kim T, et al. Case report and literature review of occupational transmission of monkeypox virus to healthcare workers, South Korea. *Emerg Infect Dis*. 2023;29(5):997-1001. doi:10.3201/eid2905.230028

36. Fink DL, Callaby H, Luintel A, et al; Specialist and High Consequence Infectious Diseases Centres Network for Monkeypox. Clinical features and management of individuals admitted to hospital with monkeypox and associated complications across the UK: a retrospective cohort study. *Lancet Infect Dis*. 2023;23(5):589-597. doi:10.1016/S1473-3099(22)00806-4

37. Miller MJ, Cash-Goldwasser S, Marx GE, et al; CDC Severe Monkeypox Investigations Team. Severe monkeypox in hospitalized patients—United States, August 10-October 10, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(44):1412-1417. doi:10.15585/mmwr.mm7144e1

38. Mitjà O, Alemany A, Marks M, et al; SHARE-NET writing group. Mpox in people with advanced HIV infection: a global case series. *Lancet*. 2023;401(10380):939-949. doi:10.1016/S0140-6736(23)00273-8

39. Higgins E, Ranganath N, Mehkri O, et al. Clinical features, treatment, and outcomes of mpox in solid organ transplant recipients: a multicenter case series and literature review. *Am J Transplant*. 2023;23(12):1972-1979. doi:10.1016/j.ajt.2023.07.016

40. Zucker J, Hazra A, Titanji BK. Mpox and HIV—collision of two diseases. *Curr HIV/AIDS Rep*. 2023;20(6):440-450. doi:10.1007/s11904-023-00682-w

41. Dashraath P, Nielsen-Saines K, Rimoin A, Mattar CNZ, Panchaud A, Baud D. Monkeypox in pregnancy: virology, clinical presentation, and obstetric management. *Am J Obstet Gynecol*. 2022;227(6):849-861.e7. doi:10.1016/j.ajog.2022.08.017

42. Nachega JB, Mohr EL, Dashraath P, et al; Mpox Research Consortium (MpoxReC). Mpox in pregnancy—risks, vertical transmission, prevention, and treatment. *N Engl J Med*. Published online August 28, 2024. doi:10.1056/NEJMp2410045

43. Schwartz DA. High rates of miscarriage and stillbirth among pregnant women with clade I mpox (monkeypox) are confirmed during 2023-2024 DR Congo outbreak in South Kivu Province. *Viruses*. 2024;16(7):1123. doi:10.3390/v16071123

44. Centers for Disease Control and Prevention. Mpox laboratory information. September 27, 2024. https://www.cdc.gov/mpox/hcp/laboratories/index.html

45. Lim CK, Roberts J, Moso M, et al. Mpox diagnostics: review of current and emerging technologies. *J Med Virol*. 2023;95(1):e28429. doi:10.1002/jmv.28429

46. US Food and Drug Administration. Xpert Mpox. Accessed September 19, 2024. https://www.fda.gov/media/165321/download

47. Damhorst GL, McLendon K, Morales E, et al. Performance of the Xpert Mpox PCR assay with oropharyngeal, anorectal, and cutaneous lesion swab specimens. *J Clin Virol*. 2024;171:105659. doi:10.1016/j.jcv.2024.105659

48. US Food and Drug Administration. Labcorp Monkeypox PCR Test Home Collection Kit. Accessed September 19, 2024. https://www.fda.gov/media/177286/download

49. Centers for Disease Control and Prevention. Mpox Vaccine Administration US map. Accessed September 21, 2024. https://archive.cdc.gov/www_cdc_gov/poxvirus/mpox/cases-data/mpx-vaccine-admin-density.html

50. Mortier C, Tissot-Dupont H, Cardona F, et al. How to distinguish mpox from its mimickers: an observational retrospective cohort study. *J Med Virol*. 2023;95(10):e29147. doi:10.1002/jmv.29147

51. Prasad S, Galvan Casas C, Strahan AG, et al. A dermatologic assessment of 101 mpox (monkeypox) cases from 13 countries during the 2022 outbreak: skin lesion morphology, clinical course, and scarring. *J Am Acad Dermatol*. 2023;88(5):1066-1073. doi:10.1016/j.jaad.2022.12.035

52. Cholli PA, Zucker JE, Vigil KJ, et al; LAMP Study Team. Life After Mpox (LAMP): post-mpox clinical sequelae with Associated psychosocial sequelae persisting >10 months after mpox at two US sites. Presented at: AIDS 2024, the 25th International AIDS Conference; July 25, 2024; Munich, Germany.

53. Chromy D, Urban N, Bauer WM, Kreuter A, Strassl R, Grabmeier-Pfistershammer K. Scars are frequently found as late sequelae in individuals affected by the 2022 mpox outbreak. *HIV Med*. Published online May 30, 2024. doi:10.1111/hiv.13678

54. Nguyen M, Doan T, Seitzman GD. Ocular manifestations of mpox. *Curr Opin Ophthalmol*. 2024;35(5):423-429. doi:10.1097/ICU.0000000000001066

55. Lee J, McLean J, Zucker J, Brandes S, Joice G. Mpox genital lesions: a large single-center experience with intermediate follow-up. *J Urol*. 2023;210(3):510-516. doi:10.1097/JU.0000000000003579

56. Chastain DB, Motoa G, Ortiz-Martínez Y, Gharamti A, Henao-Martínez AF. Characteristics and clinical manifestations of monkeypox among people with and without HIV in the United States: a retrospective cohort. *AIDS*. 2023;37(4):611-616. doi:10.1097/QAD.0000000000003449

57. Brown L, Delaney C, Hainsworth A. Monkeypox-associated proctitis and rectal wall perforation. *BMJ Case Rep*. 2023;16(1):e252168. doi:10.1136/bcr-2022-252168

58. National Institutes of Health. The antiviral tecovirimat is safe but did not improve clade I mpox resolution in the Democratic Republic of the Congo. Accessed August 15, 2024. https://www.nih.gov/news-events/news-releases/antiviral-tecovirimat-safe-did-not-improve-clade-i-mpox-resolution-democratic-republic-congo

59. Li P, Li J, Ayada I, et al. Clinical features, antiviral treatment, and patient outcomes: a systematic review and comparative analysis of the previous and the 2022 mpox outbreaks. *J Infect Dis*. 2023;228(4):391-401. doi:10.1093/infdis/jiad034

60. Americo JL, Earl PL, Moss B. Virulence differences of mpox (monkeypox) virus clades I, IIa, and IIb.1 in a small animal model. *Proc Natl Acad Sci U S A*. 2023;120(8):e2220415120. doi:10.1073/pnas.2220415120

61. Weaver JR, Isaacs SN. Monkeypox virus and insights into its immunomodulatory proteins. *Immunol Rev*. 2008;225:96-113. doi:10.1111/j.1600-065X.2008.00691.x

62. Centers for Disease Control and Prevention. Clinical considerations for pain management. Accessed September 14, 2024. https://www.cdc.gov/mpox/hcp/clinical-care/pain-management.html

63. Pepose JS, Margolis TP, LaRussa P, Pavan-Langston D. Ocular complications of smallpox vaccination. *Am J Ophthalmol*. 2003;136(2):343-352. doi:10.1016/S0002-9394(03)00293-9

64. Hyndiuk RA, Seideman S, Leibsohn JM. Treatment of Vaccinial keratitis with

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024

trifluorothymidine. *Arch Ophthalmol*. 1976;94(10):1785-1786. doi:10.1001/archopht.1976.03910040559015

65. Yu PA, Elmor R, Muhammad K, Yu YC, Rao AK. Tecovirimat use under expanded access to treat mpox in the United States, 2022-2023. *NEJM Evid*. 2024;3(10):a2400189. doi:10.1056/EVIDoa2400189

66. Karmarkar EN, Golden MR, Kerani RP, et al. Association of tecovirimat therapy with mpox symptom improvement: a cross-sectional study—King County, Washington, May-October 2022. *Open Forum Infect Dis*. 2024;11(3):ofae029. doi:10.1093/ofid/ofae029

67. Mazzotta V, Cozzi-Lepri A, Lanini S, et al. Effect of tecovirimat on healing time and viral clearance by emulation of a target trial in patients hospitalized for mpox. *J Med Virol*. 2023;95(6):e28868. doi:10.1002/jmv.28868

68. Akiyama Y, Morioka S, Tsuzuki S, et al. Efficacy and viral dynamics of tecovirimat in patients with MPOX: a multicenter open-label, double-arm trial in Japan. *J Infect Chemother*. 2024;30(6):488-493. doi:10.1016/j.jiac.2023.11.025

69. Aldred B, Lyles RH, Scott JY, et al. Early tecovirimat treatment for mpox disease among people with HIV. *JAMA Intern Med*. 2024;184(3):275-279. doi:10.1001/jamainternmed.2023.7696

70. Smith TG, Gigante CM, Wynn NT, et al. Tecovirimat resistance in mpox patients, United States, 2022-2023. *Emerg Infect Dis*. 2023;29(12):2426-2432. doi:10.3201/eid2912.231146

71. Garrigues JM, Hemarajata P, Karan A, et al. Identification of tecovirimat resistance-associated mutations in human monkeypox virus—Los Angeles County. *Antimicrob Agents Chemother*. 2023;67(7):e0056823. doi:10.1128/aac.00568-23

72. Garrigues JM, Hemarajata P, Espinosa A, et al. Community spread of a human monkeypox virus variant with a tecovirimat resistance-associated mutation. *Antimicrob Agents Chemother*. 2023;67(11):e0097223. doi:10.1128/aac.00972-23

73. Rao AK, Schrodt CA, Minhaj FS, et al. Interim clinical treatment considerations for severe manifestations of mpox—United States, February 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(9):232-243. doi:10.15585/mmwr.mm7209a4

74. Buechler CR, Anderson Z, Kullberg SA, et al. Successful treatment of recalcitrant mpox lesions with intralesional cidofovir in a patient with HIV/AIDS. *JAMA Dermatol*. 2024;160(2):235-236. doi:10.1001/jamadermatol.2023.4727

75. Adler H, Gould S, Hine P, et al; NHS England High Consequence Infectious Diseases (Airborne) Network. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *Lancet Infect Dis*. 2022;22(8):1153-1162. doi:10.1016/S1473-3099(22)00228-6

76. Quenelle DC, Prichard MN, Keith KA, et al. Synergistic efficacy of the combination of ST-246 with CMX001 against orthopoxviruses. *Antimicrob Agents Chemother*. 2007;51(11):4118-4124. doi:10.1128/AAC.00762-07

77. Thet AK, Kelly PJ, Kasule SN, et al. The use of vaccinia immune globulin in the treatment of severe mpox virus infection in human immunodeficiency virus/AIDS. *Clin Infect Dis*. 2023;76(9):1671-1673. doi:10.1093/cid/ciac971

78. Delaney KP, Sanchez T, Hannah M, et al. Strategies adopted by gay, bisexual, and other men who have sex with men to prevent monkeypox virus transmission—United States, August 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(35):1126-1130. doi:10.15585/mmwr.mm7135e1

79. Rao AK, Petersen BW, Whitehill F, et al. Use of JYNNEOS (smallpox and monkeypox vaccine, live, nonreplicating) for preexposure vaccination of persons at risk for occupational exposure to orthopoxviruses: recommendations of the Advisory Committee on Immunization Practices—United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(22):734-742. doi:10.15585/mmwr.mm7122e1

80. World Health Organization. WHO prequalifies the first vaccine against mpox. Published September 13, 2024. Accessed September 21, 2024. https://www.who.int/news/item/13-09-2024-who-prequalifies-the-first-vaccine-against-mpox

81. Centers for Disease Control and Prevention. Interim clinical considerations for use of JYNNEOS vaccine for mpox prevention in the United States. Accessed May 1, 2024. https://www.cdc.gov/poxvirus/mpox/clinicians/vaccines/vaccine-considerations.html

82. Hazra A, Rusie L, Hedberg T, Schneider JA. Human monkeypox virus infection in the immediate period after receiving modified Vaccinia Ankara vaccine. *JAMA*. 2022;328(20):2064-2067. doi:10.1001/jama.2022.18320

83. Hazra A, Zucker J, Bell E, et al; SHARE-NET writing group. Mpox in people with past infection or a complete vaccination course: a global case series. *Lancet Infect Dis*. 2024;24(1):57-64. doi:10.1016/S1473-3099(23)00492-9

84. Jamard S, Handala L, Faussat C, et al. Resurgence of symptomatic Mpox among vaccinated patients: first clues from a new-onset local cluster. *Infect Dis Now*. 2023;53(4):104714. doi:10.1016/j.idnow.2023.104714

85. Faherty EAG, Holly T, Ogale YP, et al. Notes from the field: emergence of an mpox cluster primarily affecting persons previously vaccinated against mpox—Chicago, Illinois, March 18-June 12, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(25):696-698. doi:10.15585/mmwr.mm7225a6

86. Fine PE, Jezek Z, Grab B, Dixon H. The transmission potential of monkeypox virus in human populations. *Int J Epidemiol*. 1988;17(3):643-650. doi:10.1093/ije/17.3.643

87. Rimoin AW, Mulembakani PM, Johnston SC, et al. Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo. *Proc Natl Acad Sci U S A*. 2010;107(37):16262-16267. doi:10.1073/pnas.1005769107

88. Titanji BK, Eick-Cost A, Partan ES, et al. Effectiveness of smallpox vaccination to prevent mpox in military personnel. *N Engl J Med*. 2023;389(12):1147-1148. doi:10.1056/NEJMc2300805

89. Back S, Knox B, Coakley C, et al. Effectiveness and safety of the MVA-BN vaccine against mpox in at-risk individuals in the United States (USMVAc). *Vaccines (Basel)*. 2024;12(6):651. doi:10.3390/vaccines12060651

90. Bertran M, Andrews N, Davison C, et al. Effectiveness of one dose of MVA-BN smallpox vaccine against mpox in England using the case-coverage method: an observational study. *Lancet Infect Dis*. 2023;23(7):828-835. doi:10.1016/S1473-3099(23)00057-9

91. Brousseau N, Carazo S, Febriani Y, et al. Single-dose effectiveness of mpox vaccine in Quebec, Canada: test-negative design with and without adjustment for self-reported exposure risk. *Clin Infect Dis*. 2024;78(2):461-469. doi:10.1093/cid/ciad584

92. Charles H, Thorley K, Turner C, et al. Mpox epidemiology and vaccine effectiveness, England, 2023. *Emerg Infect Dis*. 2024;30(10). doi:10.3201/eid3010.240292

93. Dalton AF, Diallo AO, Chard AN, et al; CDC Multijurisdictional Mpox Case-Control Study Group; CDC Multijurisdictional Mpox Case Control Study Group. Estimated effectiveness of JYNNEOS vaccine in preventing Mpox: a multijurisdictional case-control study—United States, August 19, 2022-March 31, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(20):553-558. doi:10.15585/mmwr.mm7220a3

94. Deputy NP, Deckert J, Chard AN, et al. Vaccine effectiveness of JYNNEOS against mpox disease in the United States. *N Engl J Med*. 2023;388(26):2434-2443. doi:10.1056/NEJMoa2215201

95. Fontán-Vela M, Hernando V, Olmedo C, et al; Spanish MPOX Vaccine Effectiveness Study Group. Effectiveness of Modified Vaccinia Ankara-Bavaria Nordic vaccination in a population at high risk of mpox: a Spanish cohort study. *Clin Infect Dis*. 2024;78(2):476-483. doi:10.1093/cid/ciad645

96. Navarro C, Lau C, Buchan SA, et al; Canadian Immunization Research Network Provincial Collaborative Network Investigators. Effectiveness of modified vaccinia Ankara-Bavarian Nordic vaccine against mpox infection: emulation of a target trial. *BMJ*. 2024;386:e078243. doi:10.1136/bmj-2023-078243

97. Ramchandani MS, Berzkalns A, Cannon CA, et al. Effectiveness of the Modified Vaccinia Ankara Vaccine against mpox in men who have sex with men: a retrospective cohort analysis, Seattle, Washington. *Open Forum Infect Dis*. 2023;10(11):ofad528. doi:10.1093/ofid/ofad528

98. Rosenberg ES, Dorabawila V, Hart-Malloy R, et al. Effectiveness of JYNNEOS vaccine against diagnosed mpox infection—New York, 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72(20):559-563. doi:10.15585/mmwr.mm7220a4

99. Wolff Sagy Y, Zucker R, Hammerman A, et al. Real-world effectiveness of a single dose of mpox vaccine in males. *Nat Med*. 2023;29(3):748-752. doi:10.1038/s41591-023-02229-3

100. Yeganeh N, Yin S, Moir O, et al. Effectiveness of JYNNEOS vaccine against symptomatic mpox disease in adult men in Los Angeles County, August 29, 2022 to January 1, 2023. *Vaccine*. 2024;42(20):125987. doi:10.1016/j.vaccine.2024.05.035

101. Hubert M, Guivel-Benhassine F, Bruel T, et al. Complement-dependent mpox-virus-neutralizing antibodies in infected and vaccinated individuals. *Cell Host Microbe*. 2023;31(6):937-948.e4. doi:10.1016/j.chom.2023.05.001

102. Rosen JB, Arciuolo RJ, Pathela P, et al. JYNNEOS effectiveness as post-exposure prophylaxis against mpox: challenges using real-world outbreak data. *Vaccine*. 2024;42(3):548-555. doi:10.1016/j.vaccine.2023.12.066

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024

103. Merad Y, Gaymard A, Cotte L, et al. Outcomes of post-exposure vaccination by modified Vaccinia Ankara to prevent mpox (formerly monkeypox): a retrospective observational study in Lyon, France, June to August 2022. *Euro Surveill*. 2022;27(50):2200882. doi:10.2807/1560-7917.ES.2022.27.50.2200882

104. UNICEF. UNICEF scales up efforts to protect children as mpox outbreak spreads in the Democratic Republic of the Congo. Accessed September 14, 2024. https://www.unicef.org/press-releases/unicef-scales-efforts-protect-children-mpox-outbreak-democratic-republic-congo

105. Katoto PD, Muttamba W, Bahizire E, et al. Shifting transmission patterns of human mpox in South Kivu, DR Congo. *Lancet Infect Dis*. 2024;24(6):e354-e355. doi:10.1016/S1473-3099(24)00287-1

106. Vakaniaki EH, Kacita C, Kinganda-Lusamaki E, et al. Sustained human outbreak of a new MPXV clade I lineage in eastern Democratic Republic of the Congo. *Nat Med*. 2024. doi:10.1038/s41591-024-03130-3. doi:10.1038/s41591-024-03130-3

107. Forni D, Cagliani R, Pozzoli U, Sironi M. An APOBEC3 mutational signature in the genomes of human-infecting orthopoxviruses. *mSphere*. 2023;8(2):e0006223. doi:10.1128/msphere.00062-23

108. O'Toole Á, Neher RA, Ndodo N, et al. APOBEC3 deaminase editing in mpox virus as evidence for sustained human transmission since at least 2016. *Science*. 2023;382(6670):595-600. doi:10.1126/science.adg8116

109. McQuiston JH, Luce R, Kazadi DM, et al; CDC 2024 Clade I Mpox Response Team. US preparedness and response to increasing clade I mpox cases in the Democratic Republic of the Congo—United States, 2024. *MMWR Morb Mortal Wkly Rep*. 2024;73(19):435-440. doi:10.15585/mmwr.mm7319a3

110. Askling HH, Gisslén M, von Schreeb J. Mpox clade I outbreak and the first European case ex Africa, in Sweden—a call for global health equity. *New Microbes New Infect*. 2024;62:101465. doi:10.1016/j.nmni.2024.101465

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 10/14/2024